

BIOMOLECULAR MODELING

in a Process Dynamics and Control Course

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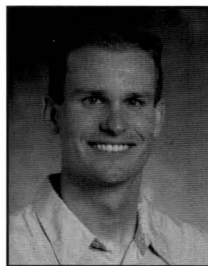
The field of chemical engineering has always been dynamic and evolving, from the field of applied industrial chemistry at the beginning of the last century, through the revolutionary reformulation of unit operations and engineering science in the 1960s, to the extensive use of computing and the incorporation of biology over the last two decades.^[1] This latter change is now maturing. Chemical engineering departments around the world are changing their names and refocusing their missions to include the fundamental science of biology.

BRINGING IN BIOLOGY

There are significant reasons biology is needed in engineering curricula. Most prominently, the human genome was declared finished (at least within a reasonable tolerance) in 2001,^[2, 3] and thus the full “parts list” of this organism and many others is now available. High-throughput and systems biology tools are extending this “parts list” to provide complex views of biological systems at the molecular and cellular level.^[4, 5] Concurrently, the pharmaceutical industry is creating new drugs and products using new biotechnology (cell culture, protein engineering, genetics). These advances rely on tools from the fields of micro- and nanotechnology, and allow us to measure and affect processes on the biological-length scales (Ångstroms to microns). Biological systems are complex, robust, specific, and tightly regulated. Many engineers are interested in mimicking these qualities in designed materials, processes, devices, and systems. In addition, we are poised to discover new insights into biology by bringing chemical engineering perspectives to the field.

Changes at JHU

At Johns Hopkins University (JHU), the Department of Chemical Engineering has long had a significant focus on biologically relevant problems, due in part to the proximity and diffusion of ideas from our prominent medical school and biomedical engineering department. Of our 12 full-time faculty, six have research programs primarily focused on biological problems (protein engineering, cell engineering, drug delivery, etc.), and most of the remaining six have projects with biological implications or applications (nanofluidics and nanodevices, self-assembly). Therefore, as discussions within the chemical engineering community began to suggest that renaming departments could be useful to the field, we immediately implemented such a change at Hopkins. Our department officially became the Department of Chemical and Biomolecular Engineering (ChemBE) in fall 2002. We also recognized that to be a department including biomolecular engineering, it is necessary to train students, both undergraduate and graduate, in this field. In practice, many Hopkins students were already receiving such training,



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as research ideas naturally diffuse into traditional courses and new electives. We resolved to critically examine our undergraduate curriculum and revise course requirements and topics within all core courses to realign the undergraduate curriculum with our new mission.

The context and purpose for these new courses can best be summed up by the new JHU ChemBE mission statement:

Our mission is to define and educate a new archetype of innovative and fundamentally grounded engineer at the undergraduate and graduate levels through the fusion of fundamental chemical engineering principles and emerging disciplines. We will nurture a passion for technological innovation, scientific discovery, and leadership in existing and newly created fields that cuts across traditional boundaries. We will be known for developing leaders in our increasingly technological society who are unafraid to explore uncharted engineering, scientific, and medical frontiers that will benefit humanity.

The Department of Chemical and Biomolecular Engineering offers courses and training toward a B.S. degree in chemical and biomolecular engineering. This discipline is dedicated to solving problems and generating valuable products from chemical and biological transformations at the molecular scale. The undergraduate program emphasizes the molecular science aspects of biology and chemistry along with engineering concepts essential to developing commercial products and processes. By selecting an appropriate concentration or by free electives, students can prepare for a professional career path or for further study in chemical, biomolecular, or a related engineering field as well as medical, law, or business school. In the tradition of JHU, many undergraduates are also involved in research—working closely with faculty and graduate students in research groups.

Changes in the Needs of a Dynamics and Control Course

With the departmental decision to change the undergraduate curriculum, I contemplated questions about the process control course. What skills and abilities of “dynamics and control” are also applicable to biomolecular and nanoscale systems? What new skills and abilities must be taught? How are biological dynamical systems similar to and different from traditional chemical process systems? How will our new graduates differ from their predecessors? Similar questions were discussed at a recent series of national workshops.^[6] As additional background has been added to the curriculum, some have even suggested that dynamics and control be

| BOX 1 Specific Course Objectives | |
|---|---|
| 1. | Create dynamic models for chemical and biological processes, including single-variable and multivariable, linear and nonlinear systems. |
| 2. | Integrate dynamic models to determine system behavior over time using Laplace methods, state space methods, or numerical methods. |
| 3. | Design control schemes to control system behavior. |
| 4. | Analyze dynamics and control with frequency approaches. |
| 5. | Analyze nonlinear dynamics with phase portraits and numerical methods. |
| 6. | Meet environmental and safety objectives through process control. |
| 7. | Use computational tools for system analysis. |
| 8. | Operate an industrial control system on a lab-scale process. |
| 9. | Collaborate in small working teams on research, analysis, and design. |
| 10. | Present work orally and in written reports. |

| BOX 2 Topics Covered | |
|---------------------------------------|--|
| 1. | Motivation for modeling and control |
| 2. | Modeling and system representations |
| 3. | State space models and linearization |
| 4. | Introduction to MATLAB |
| 5. | Pharmacokinetic modeling, biomolecular modeling, and the Central Dogma |
| 6. | Laplace transforms |
| 7. | Transfer functions |
| 8. | First, second, and higher-order systems |
| 9. | Poles and zeros, time delay |
| 10. | Empirical model formulation |
| 11. | Control of gene expression, lac operon |
| 12. | Feedback control |
| 13. | PID controllers |
| 14. | Closed-loop transfer function and stability |
| 15. | Large-scale biosimulation (guest lecture) |
| 16. | Controller tuning in industry (guest lecture) |
| 17. | Frequency response |
| 18. | Bode and Nyquist approaches, robustness |
| 19. | Introduction to nonlinear dynamics |
| 20. | Lotka-Volterra model, limit cycles, chaos |
| 21. | Current topics in the literature |

eliminated.^[7] The specialty, however, is important in biology because biological processes are dynamic, nonequilibrium, and tightly integrated and regulated as a system.^[7]

There are several main ways in which biological systems differ from traditional chemical process systems. First, chemical process systems are human-created with known parts and components. Biological systems evolve without human design, and they involve many parts and components that we are still discovering. Indeed, the fact that we are rapidly dis-

In traditional process dynamics and control courses, students learn about sensors, transducers, and actuators. In the new ChemBE curriculum, students must also examine the structures of biomolecular control components.

covering these parts and their functions now (via the genome project and various micro- and nanoscale analyses) is one of the main reasons this topic is important today. In the study of dynamics of biological systems, the task is often to reverse engineer the workings of the system, whereas in a chemical process the task is to build a model from the components and parts of a known process.^[8]

Secondly, biological systems are almost always nonlinear. Enzymatic reactions and active transport channels follow Michaelis-Menten kinetics, allosteric proteins have multistate behavior, and intracellular and tissue transport can be super- or sub-diffusive due to the structured environment. Biological systems are often complex, involving multiple length scales from the atomic and molecular through the tissue, organism, and even ecosystem level. The range of time scales is equally broad, from the fluctuations of protein molecules over nanoseconds to ecological changes over decades. Biological systems incorporate multiple regulatory loops including feedback, feedforward, and more complex control schemes.

These issues are not limited to biological systems: real chemical processes also exhibit the challenges of interplay between multiple length and time scales, nonlinear underlying equations, and multiple interacting control loops. Newer textbooks treat these subjects judiciously in later chapters.^[9-11] The utility of these topics to both biological and chemical process systems provides additional motivation to include these ideas in a new dynamics and control class.

Recent chemical engineering textbooks have begun to include biological problems and examples. For example, Bequette's text includes modules on a biochemical reactor and pharmacokinetic models for diabetic patients.^[9] Ogunnaike and Ray also include problems from pharmacokinetics, biotechnology, tissue engineering, and physiology (see problems in chapter 6 on dynamics of higher-order systems).^[10] Seborg, Edgar, and Mellichamp now include a section on fed-batch bioreactors.^[11]

In this article, I detail the ways in which I have modified the traditional process dynamics and control course to create a new course, "Modeling, Dynamics, and Control of Chemical and Biological Processes." The course is semester long, (13 weeks) with two 1.5-hour lectures and one hour-long discussion per week. It is typically taken during the senior year. It is required for ChemBE majors, and typically 25% of the students are nonmajors or part-time students from local industry. Below, I discuss the changing nature of students

observed in the new chemical and biomolecular engineering program, and detail the revisions in the syllabus, the new modules in the course, and the modifications of traditional modules. Student learning in the course is assessed through homework, exams, and a short presentation. The usefulness of course changes is assessed through a survey of alumni. I conclude with my opinions on the material that remains omitted and prospects for the future of this course in the chemical engineering curriculum.

STUDENTS

The chemical and biomolecular engineering students at JHU reflect the changing interests of the new generation entering the field, perhaps to an extreme given Hopkins' reputation in life sciences. These interests are reflected in previous courses taken by the students. Figure 1 (next page) shows the percentage of students enrolled in the dynamics class who had taken biology subjects. ChemBE majors are listed separately (nonmajors include biomedical engineering students who have taken an engineering "Molecules and Cells" course). Biochemistry became a mandatory course for the graduating class of 2007, but the classes before that showed interest in the subject, and in 2005 77% of the students had taken biochemistry. This background allows me to move more quickly through the Central Dogma of Biology and assume some knowledge from the students about the role of DNA, RNA, and proteins in the cell.

Hopkins students are highly involved in research. In fall 2005, 65% of students participated in research at some time during their tenure at Hopkins and, of those, 55% were involved in biologically related research. This background elevated the level of discussion on current engineering topics as well as on the basic elements of biological systems, and what those components do. In applying these course modifications at other schools, it may be necessary to take into account the background of the students.

SYLLABUS AND OBJECTIVES

Boxes 1 and 2 show the course objectives and the list of topics covered in the course from the syllabus. In a broad sense, the course is structured similarly to a traditional process control course: the first third of the course covers dynamics, and the second third feedback control. Both of these parts are infused with biological examples and systems, including a couple of special lectures. The last third of the course includes a new section on nonlinear dynamics, and a week

to review current modeling and control literature. Students are graded on the traditional tests and homework, and in addition they perform an experimental lab exercise and present a literature article to the class. Box 3 shows the biologically related learning objectives and those from the novel nonlinear dynamics segment.

Traditional components

Many portions of a traditional chemical process control course have been retained. In particular, the philosophies of model building, Laplace approaches, transfer functions, block diagrams, feedback control, and frequency response methods are essential. Many traditional concepts can be reinforced through biological examples from recent literature, *e.g.*, Mark Marten's lab has recently characterized experimental frequency responses of fungal cell cultures.^[12] Some of the more advanced and specialized treatments for process analysis, however, have been trimmed to make additional time for new concepts. Topics now minimized include in-depth treatments of model identification, discrete control, control methodologies such as ratio control and cascade control, and, regrettably, modern control approaches such as model-based controllers.

MAJOR REVISIONS

The major subject material additions to the course are as follows.

Central Dogma

The Central Dogma of Biology concerns the flow of information in a cell. Deoxyribonucleic acid (DNA) is transcribed by the polymerase into ribonucleic acid (RNA), and RNA is translated by the ribosome into protein. Proteins perform functions within the cell. Therefore, control in a cell can be exerted at any of these levels—interfering with transcription, translation, or the protein function directly. These systems can be modeled as a set of chemical reactions in a cascade, for example, $r_{\text{translation}}(t) = k_{\text{translation}} C_{\text{polymerase}}(t-\theta) C_{\text{mRNA}}(t-\theta)$ expresses the rate of translation of mRNA into protein, given the concentration of the polymerase and the mRNA transcript, and assuming a transcription time delay of θ . These concepts are accessible to students with training in kinetics and reactor design.

Pharmacokinetic and Pharmacodynamic Approaches

Organism models have been built using so-called pharmacokinetic approaches. In this approach, each tissue in the body (*e.g.*, brain, liver, muscle) is modeled as a one-, two-, or three-compartment chamber. The compartments are assumed to be either diffusion-limited or reaction-limited, and are modeled accordingly as an ideal system. The bloodstream is modeled as a single (or double) well-mixed compartment that connects the other organs together. The set of compartments can be distilled into a system of coupled ordinary differential equations. These models are most often used to characterize the movement of a drug or specific set of molecules around the body.^[13, 14]

Population Balances

Molecular, cellular, and ecological systems can be considered by writing population balances, or balances on the number of cells, molecules, or organisms in the system: $dN/dt = bN - dN + \Gamma$, where N is the number of units in the system, b and d are birth and death rates, and Γ represents additional fluxes in or out of the system. These types of models can describe the number of molecules inside a cellular organelle, the number of cells in a culture or tissue, or the number of organisms in an ecosystem, for example. Such equations are intuitive for a chemical engineering student with training in mass and energy balances, and they quickly allow the student to work problems with these applications. An example study in literature is the measurement of leukocyte birth and death rates using tracing with the BrdU label.^[15]

Control of Gene Expression

One of the most fundamental ways in which a cell exhibits control is by changing which genes are expressed, thus what proteins exist to carry out function.^[16] Gene expression is controlled by transcription factors—proteins that bind to the DNA and either recruit the polymerase or prevent the polymerase from initiating a transcript. The transcription factors themselves are often switches activated by the presence of a small molecule or a covalent modification. For example, the bacterial lac operon system regulates cell metabolism to use either glucose or lactose as a carbon source.^[16] When lactose is present, allolactose (a lactose derivative) binds the lac repressor, which can then dissociate from the DNA, allowing transcription of the genes encoding the proteins necessary for metabolizing lactose. In the presence of the more efficient glucose feed, however, additional proteins are regulated via the level of cyclic AMP to ensure metabolic energy is not wasted producing lactose-metabolizing machinery. Keasling's group has constructed a straightforward dynamic model of the system,^[17] and their article makes an excellent demonstration of a nonlinear, multivariable system that can be simulated using concepts, skills, and tools that students learn in the first third of a dynamics and control course.

Furthermore, this segment allows me to introduce a description of the biomolecules involved in the process. In traditional process dynamics and control courses, students learn about sensors, transducers, and actuators. In the new ChemBE curriculum, students must also examine the structures of biomolecular control components. PowerPoint slides available from publisher W.H. Freeman^[18] (Chapter 31) show the structures of molecules involved in control loops in both prokaryotic and eukaryotic cells, from the small molecule effectors, to allosteric proteins and transcription factors, to the ribosome, polymerase, and histones. With this biomolecular background, students were challenged in a homework assignment to imagine other nanoscopic implementations of a control scheme. In addition, they could predict the effect of perturbations to the existing biological system (see Box 4, page 304).

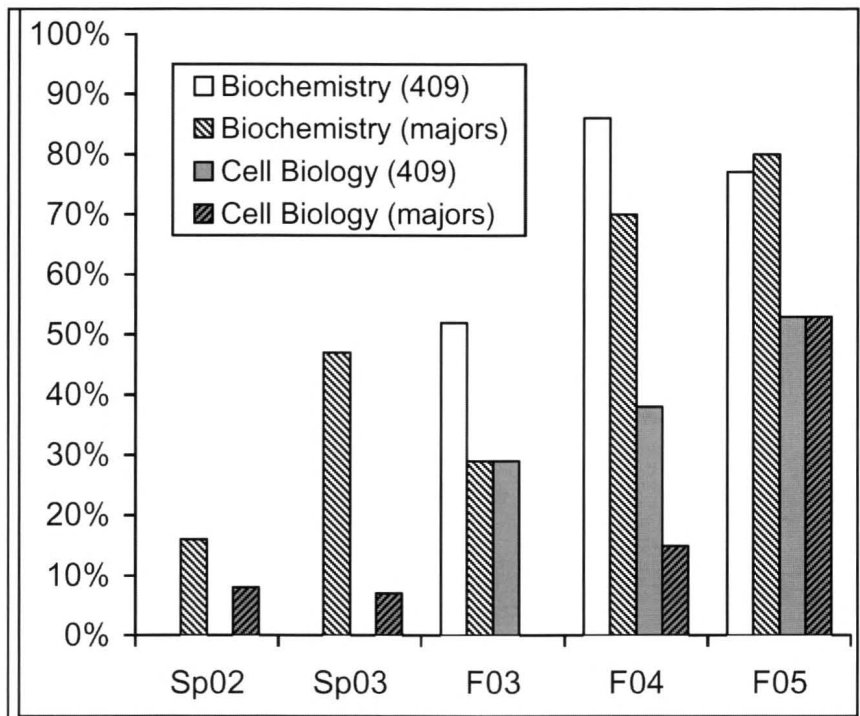
Large-Scale Biosimulation

The scope and impact of biosimulation is demonstrated by examining recent simulations by a biotechnology startup company that has published details on its models. Entelos (Daly City, CA) employs chemical engineers along with biologists, biochemists, and computer scientists to create realistic disease models. We review the idea of taking a model to the extreme using a case study of Entelos' arthritis model that simulates a rheumatoid joint. The model has hundreds of state variables and captures cell population dynamics, biochemical mediator production, cell contact of synovial fibroblasts, macrophages, T-cells, and chondrocytes. Ultimately, the model predicts cartilage degradation.^[19] With this example, we can discuss issues of numerical accuracy, experimental validation, and uncertainty.

Additional Dynamical Analysis Topics

Several fundamental skills underlie biological dynamics problems and need extra emphasis in our course. Fortunately, some of these same concepts, such as state-space representation, multivariable systems, and treatment of coupled nonlinear evolution equations, have

Figure 1: Biology-course background of students in the dynamics and control class (ChemBE 409) and for ChemBE majors only. The number of students surveyed in the course each year was 21, 29, and 31 in Fall 2003, 2004, and 2005, respectively. The number of ChemBE graduates was 12, 15, 14, 20, and 15 for the classes of 2002-2006. Students were not surveyed about their academic background in Spring 2002-2003, and data for majors are from student transcripts.



become more important in industrial process control and are more emphasized in recent textbook treatments. While Laplace approaches create elegant analytic treatments, tools such as MATLAB and Mathematica make it easy to represent vectors and create state-space representations. In particular, Bequette's recent textbook^[9] incorporates the state-space viewpoint from the beginning, introducing eigenvalue/eigenvector treatments immediately and later developing Laplace treatments. With computational tools it is a straightforward generalization to include multiple variables for inputs and outputs in a dynamic model. These approaches culminate in a unit on nonlinear dynamics at the end of the semester.

BOX 3 Nontraditional Learning Objectives

Basics of Modeling:

1. Derive population model equations for cells, molecules, or organisms.
2. Describe the approach of pharmacokinetic modeling.
3. Derive dynamic equations for compartment-based models of living organisms.

Biomolecular Control Systems:

4. Describe the lac operon as a model biomolecular control system, using standard biochemical terms properly (operator, inducer, repressor, promoter, gene, constitutive, induced).
5. Identify standard control features in biomolecular control systems.
6. Describe post-translational control strategies and eukaryotic strategies such as chromatin packing.
7. Describe the Central Dogma of Biology and identify steps where control can be achieved.
8. Imagine new complex control arrangements using biomolecular components.
9. Create complex dynamic models for biomolecular systems.

Introduction to Nonlinear Dynamics:

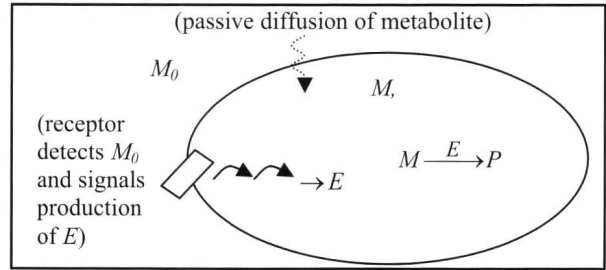
10. Analytically solve for a trajectory given initial conditions and a linear system.
11. Sketch a phase portrait for a linear system or for some nonlinear systems.
12. Identify attractors, repellers, centers, and saddles from the eigenvalues of a system near a fixed point.
13. Identify or define limit cycles and describe qualitative features of chaotic trajectories.
14. Integrate a nonlinear system using a numerical tool.

BOX 4

Sample Homework and Exam Problems in Biomolecular Modeling and Control

Population balances and compartment models

Develop a *very simple* dynamic model for an *E. coli* cell consuming a metabolite. Ultimately, we would like to know the instantaneous rate of hydrolysis of the metabolite in response to dynamic changes in the metabolite concentration outside of the cell. The hydrolysis occurs via an enzyme that is itself regulated (through molecular mechanisms in the cell) by the external metabolite concentration.



Assume the concentration of the metabolite outside of the cell, M_0 , can be manipulated dynamically. The metabolite diffuses passively into the cell. Inside the cell, an enzyme hydrolyzes the metabolite (concentration M) into a product. The enzyme (concentration E) is expressed in response to the presence of the metabolite: a receptor on the outside of the cell detects the external concentration of metabolite and signals this information to the transcription and translation machinery; for simplicity, ignore those intermediate steps and assume that the rate of enzyme production in the cell is instantaneously proportional to the concentration of the metabolite *outside* the cell. The enzyme cannot diffuse through the cell membrane and it degrades naturally with a rate of $r_d = k_d E$. The metabolite

hydrolysis obeys Michaelis-Menten kinetics, $r = \frac{kME}{K_m + M}$.

- Identify the state variable(s), input and output variable(s), and parameter(s).
- Derive model differential equations to describe this system. Define any physical parameters you need as necessary.
- Put your model in deviation variable form and linearize if necessary. You might want to replace combinations of constants with new parameters (α , β , etc.) to make your mathematics convenient, particularly as you proceed to (d).
- Find a transfer function from the input to output variable(s).

Pharmacokinetics

- Sketch a process flow diagram for a pharmacokinetic model that includes a one-compartment pancreas and a two-compartment brain, connected by the bloodstream.
- Formulate model equations for the concentrations of a molecule in the brain. Assume the flux between the two compartments is membrane-limited and passive, *i.e.*, $n = -h(C_I - C_{II}/R)$. Also, assume the molecule is degraded in the inner compartment with first-order rate constant k_d .
- Identify input and output variables and parameters for the most general model. Is your system under-, over-, or exactly determined?

Control of gene expression (adapted from Berg^[16])

A common genetic manipulation employed by cell biologists is to delete a particular gene. What would be the effect of deleting the following genes in the *lac* repressor system?

- lacY*
- lacZ*
- lacI*

Nonlinear dynamics (adapted from Beltrami^[20, 31])

Consider this coupled system of ODEs:

$$\dot{x}_1 = 9x_1 \left(1 - \frac{x_1}{9} \right) - 2x_1x_2$$

$$\dot{x}_2 = 6x_2 \left(1 - \frac{x_2}{12} \right) - x_1x_2$$

This model captures the dynamics of two competing populations of bacteria. The two state variables represent the population densities of each species, the terms in parentheses cap the growth due to limitations in the environment, and the x_1x_2 terms represent the negative effects of competition between the species.

- Show that the point $[5 \ 2]^T$ is a fixed point.
- Linearize the system around $[5 \ 2]^T$ and find the eigenvalues and eigenvectors. Is this point stable or unstable? Is the local behavior oscillatory?
- Sketch the phase portrait for this system, including the four fixed points, nullclines, and representative trajectories. Note that since the variables represent population densities, values less than zero are not meaningful and can be omitted from the diagram.
- Briefly interpret the physical meaning of the phase portrait.

BOX 5

Selected Literature Articles, Including Biological Dynamics, Suitable for Review in an Undergraduate Course

- “Robust control of initiation of prokaryotic chromosome replication: essential considerations for a minimal cell,” S.T. Browning, M. Castellanos, and M.L. Shuler, *Biotech. Bioeng.*, 88(5), 575 (2004)
- “Containing pandemic influenza at the source,” I.M. Longini Jr., *et al.*, *Science*, 309, 1083 (2005)
- “A computational study of feedback effects on signal dynamics in a mitogen-activated protein kinase (MAPK) pathway model,” A.R. Asthagiri and D.A. Lauffenburger, *Biotechnol. Prog.*, 17, 227, (2001)
- “A mathematical model of caspase function in apoptosis,” M. Fussenegger, J.E. Bailey and J. Varner, *Nat. Biotechnol.*, 18, 768 (2000)
- “Robust perfect adaptation in bacterial chemotaxis through integral feedback control,” T.M. Yi, Y. Huang, M.I. Simon and J. Doyle, *Proc. Nat. Acad. Sci.*, 97(9), 4649 (2000)

Nonlinear Dynamics

Since biological systems are often highly nonlinear and can exhibit multiple steady-state and non-steady-state behavior, I have incorporated a unit on nonlinear dynamics. We begin with a set of nonlinear, multivariable, dynamic equations, such as $\dot{x}_1 = x_2$; $\dot{x}_2 = -x_2 - \sin x_1$ which represents large motions of a forced pendulum. Approaches to these problems are covered in Beltrami’s short treatise^[20] and in a later chapter in Coughanowr’s text.^[21] We discuss the idea of multiple steady states and how a complete analysis must capture a system’s behavior throughout the phase space. We then discuss fixed points (steady states), eigenvalues (poles), and eigenvectors, relating them to concepts introduced in the Laplace framework. We proceed to sketching phase portraits of attractors, repellers, saddles, and centers. Finally, we discuss means of constructing a complete nonlinear phase portrait using nullclines and linear analysis of all fixed points.^[20] The Lotka-Volterra problem,^[22] which is usually associated with predator-prey ecological phenomena but was, in fact, first derived to analyze chemical kinetics, provides an excellent and tractable in-class problem for students to work in small groups. Discussion leads naturally to concepts of robustness (or the lack thereof in the Lotka-Volterra system) and the idea of a limit cycle. In discussing limit cycles, we review oscillating chemical systems such as the Belousov-Zhabotinsky reaction,^[23,24] for which chemical kinetic models have been constructed.^[25] Finally, in a homework assignment, students integrate the Lorenz equations to plot trajectories for a strange attractor based on the Rayleigh instability of a liquid heated from below.^[26] In the final class discussion we contrast this system’s dynamics with that of less strange attractors, and we identify the defining characteristics of chaos (*i.e.*, sensitivity to initial conditions, trajectory returning infinitely often albeit erratically to the neighborhood of each point on the attractor, fractal microstructure, and noisy power spectra). With a background in dynamics developed throughout the semester, students have an appreciation for the oddities of a chaotic system and a strange attractor, and are able to speculate how

a chaotic dynamical system might be controlled.

Literature Review

Student understanding of modeling, dynamics, and control concepts in the application to biological systems can be immediately assessed by an oral literature review. In small groups of two to three people, students review a current paper in scientific literature on the subject of modeling, dynamics, and control of a chemical or biological process. The goals are: (1) to apply knowledge of modeling and control to current applications, particularly in biomolecular and cellular applications

for which the course has relatively few homework problems during the semester; (2) to gain experience extracting relevant information from primary literature; (3) to synthesize the topics covered during the semester; and (4) to practice oral presentation skills. Talks present the basic concepts of the article, particularly the modeling and control aspects. Students need to rephrase the work into standard control terms (control objective, inputs, outputs, state variables, feedback, feedforward, stability, robustness, etc.). Short presentations and written summaries include basic background of the ap-

Class discussion, however, often clarified points and helped students recognize the motivations and strategies employed by each paper’s authors.

plication, some details on the model or controller formulation, and some of the results. The ambitious groups replicate some of the work, a simplified model, or a simple extension using MATLAB. I provide the students a list of articles in literature (see Box 5), but students are allowed to choose articles that interest them, and occasionally they contribute something from a lab where they work. Overall, students demonstrate ease in explaining the biological context of the problems and the dynamic behavior or control systems studied. Occasionally students needed help identifying proper state variables and system inputs and outputs, and some complex models in the literature were challenging for undergraduates to fully appreciate. Class discussion, however, often clarified points and helped students recognize the motivations and strategies employed by each paper’s authors. Students complete peer-assessments of the members of their team,^[27] and I evaluate

their talks, focusing on how well students learn the concepts of dynamics and control (see Box 6).

Guest Lectures

To further broaden the perspectives heard in-class, I typically include two guest lectures per semester. One is given by Red Bradley and Lochlann Kehoe of GSE Systems, a local control systems company. These engineers give an industrial perspective on the challenges and complexities of modeling and controlling real chemical process systems. The second guest lecture is given by someone involved in biological modeling, and differs each year. Two recent speakers were Prof. Kenneth Kauffman of the University of California at Davis who discussed optimal control in cellular systems,^[28] and Dr. Saroja Ramanujan of Entelos, Inc., who discussed large-scale biosimulation of arthritis.^[19] Guest lectures include a question-and-answer period, and student comprehension of the main topics is evaluated through short-answer, closed-book exam questions.

ASSESSMENT

Students complete a mid-semester survey and an end-of-semester course evaluation, both of which include questions about the usefulness of the biological content in the course. Opinions are mixed, as some students enjoy the new perspectives while others are clearly uncomfortable with the biological topics (data not shown). Resistance has decreased in recent years, probably due to a combination of changed expectations and improved teaching of the material due to past feedback. To assess the long-term effectiveness of the class, alumni from the first three offerings of the course were surveyed online. Respondents included students from the graduating classes of 2003 through 2005 currently in industry, graduate school in ChE or ChemBE, graduate school in other fields, or professional school. The survey and responses are shown

in Box 7. Overwhelmingly, the alumni felt that the addition of biological material helped make the course more practical, and prepared them for their future careers. They also felt that the course did not suffer from lack of traditional content; this view was shared by an alum working in the process control industry and another in a graduate process control research group. Anecdotally, one alumnus reported that he had vigorously opposed the integration of biology into the curriculum in his end-of-semester course evaluation and senior exit interview, but that he had experienced a complete change of heart and now is thankful for his biologically related training. Another alumnus, now a graduate student in biological and environmental engineering, noted that the study of the lac operon was specifically useful to converse with biologists and understand gene regulation. Interestingly, 62% reported that knowledge of biology is essential to their current positions, and only one respondent reported that biology is not at all needed in his or her current position.

OUTSTANDING TOPICS

Much of dynamic biological phenomena requires mathematical treatments that are significantly different from traditional, lumped-parameter, continuous, or deterministic treatments. In particular, many molecular systems are known to be stochastic and require treatments such as Fokker-Planck and Langevin equations.^[29] Recently, one institution has developed a Web module to teach stochastic modeling using batch reactor models and oscillating reactions.^[30] I have, so far, been unable to introduce this material, but perhaps as students enter with more biology background the time devoted to introducing biological concepts can be redirected toward these novel treatments. One possibility to free up additional time might be teaching dynamics entirely in state-space form and removing

BOX 6 Literature Review Evaluation of Team Oral Presentations

Assessment Questions

- (50%) Have the students demonstrated understanding of the major concepts of modeling, dynamics and control (modeling, solution of dynamic equations, nonlinearities, control, feedback, stability, robustness, validation, phase behavior, etc. as appropriate for the article)?
- (10%) Have the students demonstrated an understanding of computational tools?
- (20%) Have the students demonstrated excellent communication skills?
- (10%) Have the students demonstrated an ability to work together in teams?
- (10%) Are the students aware of contemporary issues, the impact of the work, and any professional or ethical responsibilities?

Components

Technical Content (65%):

Introduction (15%): Problem and goals explained clearly to audience

Model description (15%): Origin of model explained and significant assumptions detailed, model explained clearly to audience

Results (15%): Most significant results shared clearly, results teach something to the audience, control schemes are useful

Other Design Criteria / Broader Impacts (5%): Safety, environmental, economic, biological criteria; relate work to current knowledge in field

Reasonable responses to questions (15%)

Presentation (35%, roughly 5 points each): Overall flow and pace, organized presentation, clear and interesting slides, time limit met, reasonable energy level, participation by all group members, creativity, clear one-page summary sheet

Laplace treatments, but this could prove challenging with the absence of appropriate textbooks.

CONCLUSIONS

This paper surveys a radical revision of a chemical engineering process control course to include new material appropriate for chemical and biomolecular engineers. The revised curriculum has excited students and provided strong preparation for graduate school, professional school, or industry. I hope this description of our remolded dynamics and control class will be useful, inspiring, and perhaps help others to determine the next step in the chemical engineering curricular evolution. Brown has remarked that the transformation of a curriculum

can take a decade.^[1,6] The shift in the chemical engineering curriculum has just begun, and we will see more changes in the next few years.

ACKNOWLEDGMENTS

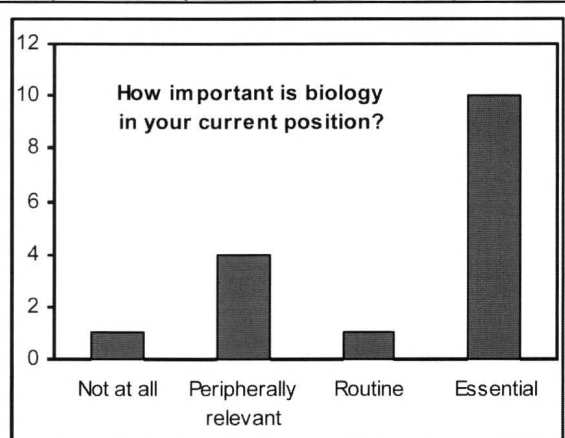
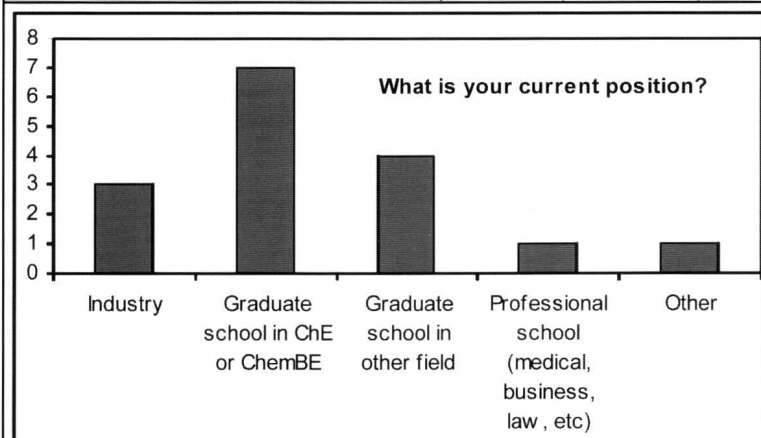
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BOX 7

Assessment Results From Alumni Survey

Sixteen alumni responded (out of 55). Respondents came from the classes of 2003 (5), 2004 (7), and 2005 (3). Largest responses indicated in bold.

| "Rate your agreement with the following statements." | N/A | 1—strongly disagree | 2—disagree | 3—neutral | 4—agree | 5—strongly agree | Response Average |
|--|---------|---------------------|----------------|-----------|-----------------|------------------|------------------|
| 1. I am comfortable with my process dynamics, modeling, and control background from the Chemical & Biomolecular Engineering Department at JHU. | 0% (0) | 0% (0) | 6% (1) | 12% (2) | 50% (8) | 31% (5) | 4.06 |
| 2. I feel this course has prepared me for the challenges I have encountered with modeling, dynamics, and control after leaving JHU. | 6% (1) | 0% (0) | 6% (1) | 19% (3) | 38% (6) | 31% (5) | 4.00 |
| 3. I feel this course shortchanged me by omitting key concepts from classical dynamics and control. | 19% (3) | 19% (3) | 44% (7) | 6% (1) | 12% (2) | 0% (0) | 2.15 |
| 4. The integration of biology helped to make the concepts of the course more practical. | 6% (1) | 0% (0) | 6% (1) | 12% (2) | 31% (5) | 44% (7) | 4.20 |
| 5. The integration of biology helped to make the concepts of the course more intuitive. | 6% (1) | 0% (0) | 12% (2) | 12% (2) | 44% (7) | 25% (4) | 3.87 |
| 6. The integration of biology helped prepare me for my career or education after my B.S. in ChemBE. | 6% (1) | 6% (1) | 0% (0) | 12% (2) | 31% (5) | 44% (7) | 4.13 |
| 7. I have developed an appreciation for the challenges of analyzing complex dynamics and regulation in biological and chemical systems. | 6% (1) | 0% (0) | 6% (1) | 0% (0) | 62% (10) | 25% (4) | 4.13 |
| 8. I feel I lack a sufficient foundation from JHU in dynamics, modeling, and control to be successful at the types of tasks required of me in my current position. | 6% (1) | 25% (4) | 38% (6) | 6% (1) | 19% (3) | 6% (1) | 2.40 |



Additional course material can be accessed at <graylab.jhu.edu/courses/540.409>.

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